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BURNS DOANE SWECKER & MATHIS L L P			STRZELECKA, TERESA E	
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DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

8/12

Office Action Summary

Application No.

09/865,553

Applicant(s)

RITTNER ET AL.

Examiner

Teresa E Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3 and 6-16 is/are pending in the application.
- 4a) Of the above claim(s) 15 and 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3 and 6-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to an amendment filed February 9, 2004. Claims 1-16 were previously pending, with claims 4, 15 and 16 withdrawn from consideration. Applicants amended claim 1 and cancelled claims 2, 4, 5. Claims 1, 3, 6-16 are pending, with claims 15 and 16 withdrawn from consideration. Claims 1, 3 and 6-14 will be examined.
2. Note to Applicants about the status of claim 15: Applicants indicated that claim 15 was "previously presented", whereas the status of the claim is "withdrawn". Therefore, the amendment does not comply with the current requirements, but will be examined for the sake of advancing the prosecution.
3. Applicants' amendments overcame the following rejections: rejection of claims 1-3, 6-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by Ohmori et al. and the rejection of claims 9 and 14 under 35 U.S.C. 103(a) over by Ohmori et al. and Smith et al. Applicants' cancellation of claim 5 overcame the rejection of this claim under 35 U.S.C. 103(a) over Smith et al. and Wyman et al. The rejection of claims 1, 6, 8, 9 and 14 under 35 U.S.C. 103(a) over Smith et al. and Wyman et al. are maintained for reasons given in the "Response to Arguments" section below.
4. This office action is made non-final because of new grounds for rejection of claims 3, 7 and 10-13.

Drawings

5. The drawings (Fig. 11A) were received on February 9, 2004. These drawings are accepted. Applicants' amendments to the specification overcame the objection to drawings from the previous office action. The objection is withdrawn.

Specification

6. Applicants' amendments to the specification overcame the objections presented in the previous office action, and they are therefore withdrawn.

Response to Arguments

7. Applicant's arguments filed February 9, 2004 regarding the rejection of claims 1, 6, 8, 9 and 14 under 35 U.S.C. 103(a) over Smith et al. and Wyman et al. have been fully considered but they are not persuasive.

Applicants' only argument is that neither Smith et al. nor Wyman et al. teach SEQ ID NO: 2, and there is no motivation to combine the two references. Applicants do not indicate why it is improper to combine the two references.

Applicants' peptide with SEQ ID NO: 2 has the following sequence: GLFKALLKLLKSLWKLLLA. As indicated in the previous office action, Smith et al. teach a JTS-1 peptide with the following sequence: GLFEALLELLESLWELLLEA, i.e., the only difference between the peptide of Smith et al. and Applicants' peptide of SEQ ID NO: 2 is a substitution of glutamic acid residues with lysines. However, Smith et al. teach that the glutamic acids of JTS-1 could be replaced with basic amino acids (page 10, lines 28-30) and that lytic activity of the peptide can be controlled by introduction of lysine, arginine and histidine into the hydrophilic phase of JTS-1 (page 11, lines 9-11). Further, Wyman et al. teach conversion of an anionic peptide GALA, which contains six glutamate residues on the hydrophilic face of its helical structure with KALA, which contains seven lysine residues on the hydrophilic face of its helical structure (Fig. 1), so that the modified peptide had a net positive charge (page 3012, second paragraph). The peptide caused membrane destabilization in liposomes in the absence of DNA (page 3012, fourth paragraph) and in the presence of DNA oligonucleotides (page 3012, last paragraph; page 3013, first paragraph; Fig.

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3). Complexes of fluorescently-labeled oligonucleotides complexed with KALA were efficiently taken up by cell nuclei, in contrast to similar complexes made with GALA (Fig. 7). Therefore, Wyman et al. teach that substitution of glutamates by lysines leads to improved properties of a peptide in terms of its ability to condense DNA and deliver it to the cells, providing ample motivation for one of skilled in the art to do the same with the peptide of Smith et al., especially since Smith et al. already suggest changing glutamates to positively charged residues, such as lysines.

The rejection is maintained.

Specification

8. The abstract of the disclosure is objected to because of legal phrase "said peptide" in line 3. Correction is required. See MPEP § 608.01(b).

Claim interpretation

9. "Cationic peptide" is interpreted as a peptide with a net positive charge. "Anionic substance" is interpreted as any compound with a negative charge.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 1, 3 and 6-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 96/40958; cited in the IDS and in the previous office action) in view of Wyman et al. (Biochemistry, vol. 36, pp. 3008-3017, 1997; cited in the IDS and in the previous office action).

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A) Regarding claim 1, Smith et al. teach peptides (page 9, lines 34-37; page 10, lines 1-18; page 34, lines 10-35; page 35, lines 1-15) which are capable of membrane disruption (page 39, lines 20-36; page 40-42; page 43, lines 1-7).

Regarding claim 3, Smith et al. teach a peptide JTS-1 with amino acid sequence of GLFEALLELLESLWELLLEA and a molecular weight of 2301.8, which is less than 5 kD (page 10, line 18; page 34, line 11).

Regarding claim 6, Smith et al. teach a complex for transferring an anionic substance into a cell, the complex comprising JTS-1 and an anionic substance (= DNA plasmid) (page 43, lines 29-36; page 44, lines 1-15).

Regarding claim 6, Smith et al. teach a complex for transferring an anionic substance into a cell, the complex comprising JTS-1 and an anionic substance (= DNA plasmid), and further comprising:

(iii) at least one ligand capable of cell-specific or nuclear targeting (Smith et al. teach a surface ligand, capable of binding to cell surface receptor, and a nuclear ligand, capable of recognizing and transporting nucleic acid through nuclear membrane (page 8, lines 25-37; page 45, lines 13-27).); and/or

(v) at least one cationic compound selected from the group consisting of cationic lipids and cationic polymers (Smith et al. teach a complex with an additional binding molecule bound to the nucleic acid (page 9, lines 20-33), the binding molecule being a cationic peptide K8 (page 14, lines 2-12), or other cationic polymers such as spermine and its derivatives, spermidine, histones, polyamines, polylysine, etc. (page 15, lines 10-27).); and/or

(vi) at least one colipid (Smith et al. teach complexes of JTS-1 with liposomes (page 39, lines 20-22).).

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Regarding claim 8, Smith et al. teach the anionic substance being nucleic acid (= DNA plasmid) (page 43, lines 29-36; page 44, lines 1-15).

Regarding claim 9, Smith et al. teach the complex in which a nucleic acid comprises a therapeutically useful gene sequence and elements enabling its expression, namely, a nucleic acid encoding LDL-receptor under the control of CMV enhancer and promoter elements. LDL-receptor deficiency leads to coronary atherosclerosis and myocardial infarction (page 63, lines 5-36).

Regarding claim 10, Smith et al. teach complexes with a size of less than 200 nm, which is less than 500 nm (page 56, lines 20-24; Fig. 12a).

Regarding claim 11, Smith et al. teach complexes with a size between 20 and 100 nm (Fig. 12a, complexes with JTS-1/DNA ratio of 0.1, for example).

Regarding claims 12 and 13, Smith et al. teach complexes where the ratio of positive charges to negative charges is 0.66 to 0.7 or 1:1 (page 47, lines 29-35; page 54, lines 31-37).

Regarding claim 14, Smith et al. teach a composition comprising the nucleic acid-peptide complex (= nucleic acid transporter) and an amorphous powder, PVP, for administration by inhalation (page 67, lines 4-14 and 28-36).

B) Smith et al. do not teach cationic peptides. Smith et al. teach that the glutamic acids of JTS-1 could be replaced with basic amino acids (page 10, lines 28-30) and that lytic activity of the peptide can be controlled by introduction of lysine, arginine and histidine into the hydrophilic phase of JTS-1 (page 11, lines 9-11). The only difference between JTS-1 and SEQ ID NO: 2 is replacement of glutamates (E) with lysines (K) (see sequence alignment).

C) Wyman et al. teach conversion of an anionic peptide GALA, which contains six glutamate residues on the hydrophilic face of its helical structure with KALA, which contains seven lysine residues on the hydrophilic face of its helical structure (Fig. 1), so that the modified peptide

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had a net positive charge (page 3012, second paragraph). The peptide caused membrane destabilization in liposomes in the absence of DNA (page 3012, fourth paragraph) and in the presence of DNA oligonucleotides (page 3012, last paragraph; page 3013, first paragraph; Fig. 3). Complexes of fluorescently-labeled oligonucleotides complexed with KALA were efficiently taken up by cell nuclei, in contrast to similar complexes made with GALA (Fig. 7). In addition, plasmid DNA was efficiently transfected into cells when complexed with KALA (Fig. 8).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have made the substitution of glutamates for lysines according to Wyman et al. in the peptide of Smith et al. The motivation to do so, provided by Wyman et al., would have been that such a peptide not only destabilized membranes, but also bound DNA and mediated gene transfer into cells (page 3015, fifth paragraph). In addition, positively charged peptide effectively disrupted both neutral and negatively charged membranes (page 3016, fifth paragraph). Finally, as stated by Wyman et al. "We have designed and synthesized a novel peptide capable of condensing DNA and causing membrane leakage, nuclear delivery of oligonucleotides, and transfection of plasmid DNA in various cell lines. This peptide has a number of advantages over previously reported gene delivery systems. First, it is convenient to synthesize; second, it is efficient at mediating transfection in cells without the need for other agents such as chloroquine or adenoviral endosomal disruption agents. It provides a starting point for additional improvements in the sequence that might provide ligands for cell surface or cytoplasmic receptors to improve DNA trafficking into and through the target cell. Finally, it can serve as a platform to help unravel the roles of DNA binding/dissociation and membrane destabilization in the transfection process." (page 3016, last paragraph).

12. No claims are allowed.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
April 21, 2004


JEFFREY FREDMAN
PRIMARY EXAMINER